Hereditary angioedema caused by missense mutations in the factor XII gene: Clinical features, trigger factors, and therapy

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Background: Hereditary angioedema caused by mutations in the factor XII gene is a recently described disease entity that occurs mainly in women. It differs from hereditary angioedema caused by C1 inhibitor deficiency.

Objective: To assess the clinical symptoms, factors triggering acute attacks, and treatments of this disease.

Methods: Thirty-five female patients with hereditary angioedema and the factor XII mutations p.Thr309Lys and p.Thr309Arg who came from 13 unrelated families were studied. The observation period was 8.4 years on average (range, 2-26 years).

Results: Patients had on average 12.7 ± 7.9 angioedema attacks per year. Recurrent facial swellings occurred in all patients; skin swellings other than facial, abdominal pain attacks, tongue swellings, and laryngeal edema occurred less frequently. Some factors that triggered angioedema attacks were trauma, physical pressure, and emotional stress. Clinical symptoms started mainly after intake of oral contraceptives (17 women) or pregnancy (3 women). Exacerbation of the symptoms occurred after oral contraceptive use (8 women), pregnancy (7 women), hormone replacement therapy (3 women), intake of angiotensin-converting enzyme inhibitors (2 women), and an angiotensin 1 receptor blocker (1 woman). Effective treatments included C1 inhibitor concentrate for angioedema attacks (6 women) and, for prophylaxis, progesterone (8 women), danazol (2 women), and tranexamic acid (1 woman). No difference between mutation p.Thr309Arg and p.Thr309Lys was found.

Conclusions: Facial swelling is a cardinal symptom of this condition. Estrogens may have a great influence, but this influence is highly variable. Various treatment options are available. (J Allergy Clin Immunol 2009;124:129-34.)

Key words: *Angioedema, hereditary angioedema, hereditary angioedema type III, factor XII, coagulation factor XII gene mutation, estrogens, progesterone, danazol, tranexamic acid, C1 esterase inhibitor*

Abbreviations used

ACE-I:	Angiotensin-converting enzyme inhibitor
aPTT:	Activated partial thromboplastin time
C1-INH:	C1 esterase inhibitor
FXII:	Coagulation factor XII
HAE:	Hereditary angioedema
HAE–C1-INH:	Hereditary angioedema caused by C1-INH deficiency
HAE-FXII:	Hereditary angioedema caused by mutations in the coagulation factor XII gene
HRT:	Hormone replacement therapy
OC:	Oral contraceptive
TAT:	Thrombin-antithrombin complex

Hereditary angioedema (HAE) is characterized by recurrent angioedema attacks in various organs, leading mostly to skin swellings, severe abdominal pain attacks, and potentially life-threatening laryngeal edema.[1,2] Until recently, it was assumed that HAE represents a single disease entity and that all patients have a genetically determined deficiency of functional C1 esterase inhibitor (C1-INH).[3] The gene coding for C1-INH is located on the long arm of chromosome 11. In 2000, we described a new type of HAE that occurred in women and was not associated with a C1-INH deficiency.[4] We termed the disease *hereditary angioedema with normal C1-INH* or *hereditary angioedema type III* (HAE type III). Subsequently, more families were reported in which all affected individuals were women.[5-11] In other families, men also were affected.[12-14]

In May 2006, we identified causative mutations in 6 index patients of 20 families and in 22 patients who were members of the corresponding 6 families: 2 different missense mutations were verified as being responsible for the disease according to the cosegregation pattern.[15] These mutations show the same locus, 5q33-qter of the Hageman factor or coagulation factor XII (FXII) gene on chromosome 5 (Online Mendelian Inheritance in Man #610619). One mutation leads to a threonine-to-lysine substitution (p.Thr309Lys) and the other to a threonine-to-arginine substitution (p.Thr309Arg).[15] The mutations were located on the exon 9. Later, the presence of 1 of these mutations (p.Thr309Lys) was observed in affected individuals of additional families.[9,14,16,17]

Because the 2 mutations in the factor XII gene were found only in some families with HAE type III but not in others, we now can distinguish the following forms of HAE: (1) HAE caused by a genetic C1-INH deficiency (HAE–C1-INH; with a subtype I and subtype II, numerous mutations); (2) HAE caused by the 2 known mutations in the FXII gene (HAE-FXII); and (3) HAE-unknown—that is, HAE with an unknown genetic cause (normal C1-INH activity in plasma, no causative mutation in the gene coding for C1-INH, and neither of the known FXII gene mutations [p.Thr309Lys or p.Thr309Arg]).

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Disclosure of potential conflict of interest: The authors have declared that they have no conflict of interest.

Received for publication December 10, 2008; revised March 5, 2009; accepted for publication March 27, 2009.

Available online May 28, 2009.

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0091-6749/$36.00

doi:10.1016/j.jaci.2009.03.038

Until now, we had observed 13 families with HAE and the mutations p.Thr309Lys or p.Thr309Arg in the FXII gene. The aim of this study was to describe this new and now molecularly defined condition, HAE-FXII, including clinical signs and symptoms, the factors that trigger angioedema attacks, and treatment methods in 35 affected members of those families who carry 1 of the 2 mutations. Clinical symptoms of 23 patients included in our study have been discussed.[13] Because of the strong prevalence of the female sex in the phenotype of this autosomal-dominant inherited condition, a focus of our current study was on the investigation of the interaction of estrogens with disease activity.

METHODS

Design

Our analysis was based on partly prospective and partly retrospective clinical case reports. Data were generated by asking patients about clinical symptoms, the course of disease, trigger factors, and treatment of HAE. Documentation was accomplished through the use of standardized questionnaires. Within the prospective part, the patients were surveyed for 8.4 years on average with a range of 2 to 26 years. When the patients were seen for the first time, they were asked about the onset of the first episode and the frequency of edema episodes per year and possible factors that provoked the attacks. This interview constituted the retrospective part of the study. The visit included a physical examination and laboratory confirmation of the diagnosis of HAE. Later, the patients were seen every 4 to 6 months. In the follow-up examinations, the number of bouts of angioedema was determined by questioning the patients and by analyzing a swelling calendar that the patients filled out at home noting time, duration, and severity of their angioedema episodes and the organs involved. Data about clinical features and trigger factors come from the retrospective and prospective periods; data about treatments come exclusively from the prospective period.

Diagnosis

Patients were surveyed at the angioedema outpatient service at the Department of Dermatology, University of Mainz, Germany. Diagnosis of HAE-FXII was based on personal history (recurrent angioedema attacks and no urticaria), family history revealing other affected family members, plasma examination (C1-INH activity normal or slightly decreased), and genetic tests positive for FXII mutation p.Thr309Lys or p.Thr309Arg.

Laboratory

C1-INH activity was determined by using the chromogenic substrate C_2H_5CO-Lys(e-Cbo)-Gly-Arg-pNA (Technochrom C1-Inhibitor; Technoclone, Vienna, Austria). Plasma levels of C4 antigen were assayed by radial immunodiffusion (NOR Partigen C4; Siemens Healthcare Diagnostics, Marburg, Germany). Fibrinogen, D-dimer, thrombin-antithrombin complexes (TATs), and activated partial thromboplastin time (aPTT) were determined by using routine methods. Molecular analysis for identification of the mutation has been described elsewhere.[15] Samples were taken during attack-free intervals.

RESULTS

Heredity

We tested 53 families with HAE and normal or slightly decreased C1-INH activity for the FXII gene mutations p.Thr309Lys and p.Thr309Arg; we identified 1 of these mutations in 13 of 53 (24.5%) unrelated families. The FXII gene mutation p.Thr309Lys was found in 11 families and p.Thr309Arg in 2 families. According to the pedigrees and the available information, 53 patients out of those 13 families had clinical symptoms of HAE-FXII (Fig 1). Seven women already were deceased, with 2 of them suffocating within 8 hours from an acute upper airway obstruction, 1 at age 42 years, the other at age 38 years. Genetic information was obtained for 35 patients, all female, who made up our study group. Thirty-two patients carried the mutation p.Thr309Lys and 3 the mutation p.Thr309Arg. The mean age at the end of the study (June 2008) was 48.3 ± 21.4 years (range, 14-84 years). The patients with HAE-FXII came from 2 to 4 generations per family. Fig 2 shows the pedigree of 1 of the families and demonstrates the autosomal-dominant inheritance of HAE-FXII. One individual in each of 5 families and 2 individuals in each of 2 families had no HAE symptoms but had affected parents and children. Seven of those 9 symptom-free transmitters were men, and 2 were women.

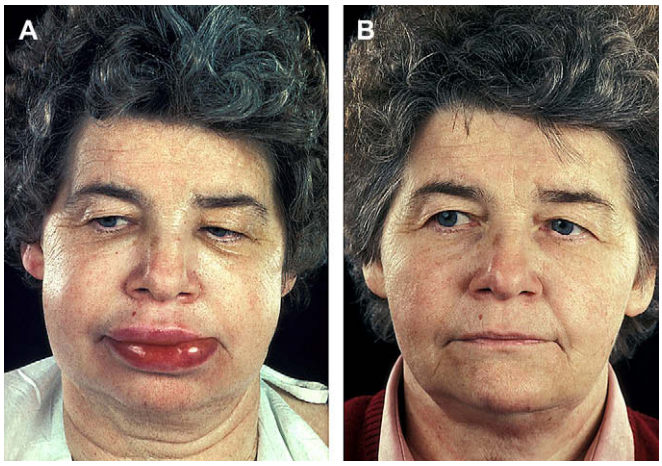

FIG 1. Swelling of the lips **(A)** and normal state **(B)** in a woman with HAE-FXII.

Onset and course of the disease

The earliest onset of clinical symptoms occurred at age 6 years in a now 14-year-old girl and started with recurrent attacks of abdominal pain. The onset of her skin swellings was in her 12th year of life. Fig 3 shows that in most patients, clinical symptoms started in the second decade of life. In total, the number of patient-years between the onset of the first symptoms and the end of the study was 978. During this period, there were 512 symptomatic years—that is, 14.6 years (SD, 15.4) on average per patient (range, 1-57).

Clinical symptoms

Skin swellings, abdominal pain attacks, tongue swellings, laryngeal edema, and edema of the uvula or the whole soft palate occurred. The affected organs and skin sites are shown in Table I. Most attacks were skin swellings. All patients had facial swellings. One patient had approximately 40 abdominal attacks that were accompanied by severe circulatory symptoms. In 2 of the attacks, the patient collapsed and fell down on the floor on the way to the restroom; in another, she lost consciousness for about 1 minute. Another woman experienced similar collapses in about 30 abdominal attacks, with loss of consciousness for several minutes in 2 of them. In 3 women, ascites were found during 4, 3, and 1 abdominal attack, respectively, with amounts of fluid between 1.5 and 2 L. In 4 women, appendicitis was assumed, and the patients unnecessarily underwent appendectomy. In 1 patient, a laparoscopy was performed, also unnecessary.

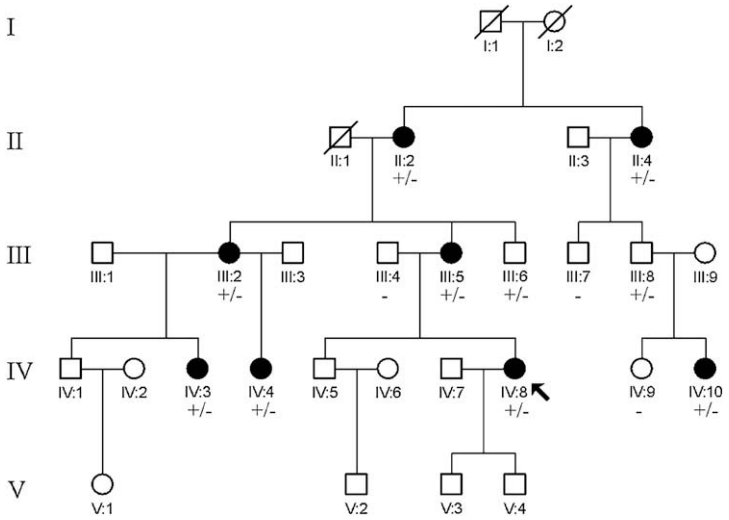

FIG 2. Pedigree of a family with HAE-FXII showing an autosomal-dominant inheritance. *Filled symbols,* Individuals affected by recurrent angioedema. +/−, Heterozygous presence of the p.Thr309Lys mutation. −, Absence of the mutation. Individual IV:8 *(arrow)* is the index patient. Individual III:8 is an unaffected male transmitting the disease.

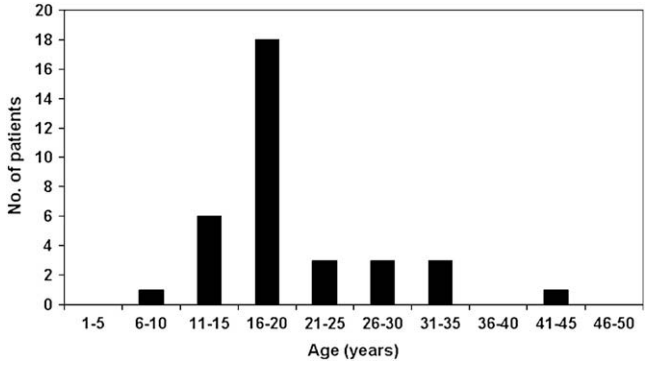

FIG 3. Age at onset in 35 patients with HAE-FXII.

Among a total of 86 tongue swellings, 44 affected only the tongue, whereas the others were associated with laryngeal edema (38 episodes) or uvula swellings (4 episodes). In total, 74 episodes of laryngeal edema occurred, 3 of them requiring an intubation. In 1 case, intubation was impossible because of the massive swelling, and an emergency tracheotomy had to be performed. That case involved tongue, pharyngeal, and laryngeal swellings that occurred after intake of angiotensin-converting enzyme inhibitors (ACE-Is). Among the 13 families, no deaths by suffocation occurred during the observation period. None of the patients ever had hives or an erythema marginatum.

Frequency of edema episodes

The mean frequency of angioedema attacks per symptomatic year was 12.7 (SD, 7.9 years; range, 1-30). The frequency of the total number of angioedema attacks varied to a high degree among the patients: one woman, now 67 years old, experienced only 1 (facial) swelling until the end of the study; another woman, currently 78 years old, experienced 1300 angioedema attacks in 64 symptomatic years. Moreover, the variability of the attack frequency within the same families was high: one woman, now 84 years old, had 1 swelling (a facial swelling) until the end of the study. Another woman from the same family, now age 59 years, had approximately 270 angioedema attacks until the end of the study.

Factors inducing the onset of clinical symptoms

In 15 of 35 patients, the first clinical symptoms started without any recognizable triggering factor—in 10 of these 15 women, within the second decade of life. In the other 20 women, the symptoms started after the initiation of oral contraceptive (OC) use or during the first pregnancy (Table II).

Factors triggering angioedema attacks

Eighteen of 35 patients reported swellings after an acute trauma: skin swellings occurred after a bump—for instance, by a volleyball or by a dog. Twelve of 35 patients reported that some of their skin swellings occurred after physical pressure (hand swellings after carrying heavy shopping bags or other heavy objects, doing gardening, or biking). Patients reported foot swellings, especially of the soles. (After walking with thin-soled shoes, the patients felt like they were "walking on eggs.") Facial swellings occurred in 7 patients after dental procedures. Tongue swellings occurred after dental procedures or a bite on the tongue. In 3 patients, after the period of spontaneous swellings (caused by OC, pregnancy, or hormone replacement therapy [HRT] or outside of these high-estrogen periods), all further swellings were pressure-induced or trauma-induced and occurred for 5, 8, and 24 years, respectively, as the only residual symptom. Skin swellings also were provoked in 1 case by exposure to cold and in another case by insect stings.

Some of the abdominal attacks of 3 patients were provoked by the eating of onions, garlic, leeks, or paprika. Eleven patients reported emotional stress as a trigger factor. In 1 patient, nearly all attacks were related to the menstrual cycle and occurred within 1 week before menstruation; in 3 other patients, this was true only for some attacks. Infectious diseases and ovulation were additional but rare trigger factors.

TABLE I. Distribution of edema episodes in various organs and skin regions in HAE-FXII on a per-patient and a per-episode basis

Attack sites	Patients, n (%)	Attacks, n (%)
Skin (total)	35 (100)	4070 (62.2)
Face	35 (100)	1506 (37.0)
Extremities	19 (54.3)	2530 (62.2)
Genitals	5 (14.2)	27 (0.7)
Neck	3 (8.6)	7 (0.2)
Stomach/gut	20 (57.1)	2267 (34.6)
Tongue	14 (40.0)	86 (1.3)
Larynx	12 (34.3)	74 (1.1)
Uvula	11 (31.4)	50 (0.8)
Total	35 (100)	6547 (100)

TABLE II. Influence of oral contraceptives, pregnancies, and hormone replacement therapy on HAE-FXII in 35 women

	Intake of OCs, n (%)	Pregnancy, n (%)	Receiving HRT, n (%)
Induction of the first clinical symptoms of HAE-FXII	17 (63.0)	3 (12)	0 (0)
Exacerbation of the pre-existing symptomatic HAE-FXII	8 (29.6)	7 (28)	3 (42.9)
No influence	2 (7.4)	10 (40)	4 (57.1)
Improvement of symptoms	0 (0)	5 (20)	0 (0)
Totals	27 (100)	25 (100)	7 (100)

Factors increasing the frequency of attacks

Estrogens. The influence of OC, pregnancy, and HRT is shown in Table II. A total of 27 women had ever tried OC, and 12 changed OC preparations 2 to 6 times, always with the same sequelae. Of the 25 women who were pregnant 1 or more times, 10 reported that their pregnancies had no influence on the course of their HAE. Another 5 patients reported that they were surprised that they had no angioedema attacks during any of their pregnancies. One patient reported that she was always happy to be pregnant because she did not have "the bothersome swellings" during the periods of all 3 of her pregnancies.

In 8 women, clinical symptoms were limited to periods in which they took OC. In 1 woman, the symptoms were limited to the periods of her pregnancies. One woman had angioedema attacks only during her pregnancy and during the period of HRT. Thus, in 10 of 35 patients, the attacks were present exclusively during high-estrogen states—that is, during the intake of OC, during pregnancy, and/or in the period of HRT. An additional patient had spontaneous swellings during the intake of OC and her 2 pregnancies; thereafter, all her 56 skin swellings were pressure-induced or trauma-induced. Another woman had swellings during OC and her 2 pregnancies. Later, only 1 skin swelling occurred, after a wasp sting.

Six women never took OC and never received HRT. Two of them, who were 14 and 18 years old, respectively, had never been pregnant, but had 19 and 3 angioedema attacks, respectively. The other 4 women in this group had been pregnant a total of 13 times (range, 1-4 pregnancies). Three of these 4 individuals reported that all their angioedema attacks occurred outside their 11 pregnancies (ie, no OC, no HRT, no attacks during pregnancies). Among 12 postmenopausal women who were older than 60 years, 4 still had skin swellings and/or abdominal attacks.

Blockers of the renin-angiotensin system (ACE-I and angiotensin II receptor blockers). Two patients received ACE-I. A now 81-year-old woman had recurrent lip, hand, and tongue swellings only during her 3 pregnancies. Twenty-nine symptom-free years after her last pregnancy, she received quinapril because of arterial hypertension. Four months after commencing quinapril intake, this individual had recurrent skin and tongue swellings; after 11 months' intake of quinapril, she developed an upper airway obstruction that required an emergency tracheotomy. Six symptom-free years later, she again received an ACE-I, ramipril, and subsequently experienced 5 severe tongue swellings. This patient now has been treated with valsartan for 7 years and has had no additional HAE symptoms. Another woman, 67 years old, started taking quinapril at age 64 years; subsequently, she had extended and more frequent skin swellings of her face, hands, and feet. A now 70-year-old woman had a considerable worsening of her HAE-FXII after intake of the angiotensin II receptor blocker losartan.

Laboratory results

As shown in Table III, C1-INH activity was lower than normal in 6 of 35 women, as was the complement component C4 in 5 women. Fibrinogen, D-dimer, and TATs were increased in some patients, and aPTT was shortened in 3 patients (Table III).

Treatment of acute angioedema attacks

Twenty-seven patients received corticosteroids for 186 attacks, and 15 patients received antihistamines for 67 attacks; these treatments were not effective. Seven patients received C1-INH concentrate (Berinert P; CSL Behring, Marburg, Germany) for 63 angioedema attacks. One patient who received Berinert P (500 U) once for an abdominal attack reported that it was not effective. In the other 6 patients, Berinert P was very or moderately effective.

Prophylactic treatment

Progesterone. Eight patients received a progesterone-containing and estrogen-free OC. Seven of them took desogestrel, which is a progestagen, for 1 to 6 years, 27 years in total. One of them shifted to an implant with etonogestrel for 3 years. Another woman received injections of medroxyprogesterone for 3 years. The 8 women were symptom-free during the period of progesterone treatment.

Danazol. One woman received 200 mg danazol, an attenuated androgen, daily for 12 years. During this time she was symptom-free. Twice the patient discontinued danazol; each cessation was followed by a series of severe abdominal attacks, tongue swellings, and skin swellings, so that the patient resumed taking danazol. As of now, no side effects have occurred. Another patient who had severe HAE symptoms and therefore received 100 mg danazol per day for 6 years was also symptom-free during that period. Later, the dose was tapered down; during the 2 years between discontinuance and the present, no more symptoms have occurred.

Tranexamic acid. Three years ago, 1 woman started treatment with tranexamic acid, 4 g per day, and has had no attacks since then.

We did not find major differences concerning clinical symptoms, trigger factors, or treatments in the 3 patients who had the

TABLE III. Laboratory results in 35 women with HAE-FXII during attack-free intervals (citrated plasma)

	Patients, n (%)	Mean	SD	Range
C1-INH activity normal (%)	29 (82.9)	86.2	13.9	71-120
C1-INH activity decreased (<70%) (%)	6 (17.1)	60.4	5.6	51-69
C4 normal (g/L)	30 (85.7)	0.34	0.10	0.22-0.54
C4 decreased (<0.20 g/L) (g/L)	5 (14.3)	0.13	0.04	0.08-0.19
Fibrinogen normal (mg/dL)	23 (65.7)	253.1	36.6	196-343
Fibrinogen increased (>350 mg/dL) (mg/dL)	12 (34.3)	414	53.6	369-546
D-dimer normal (mg/L)	25 (71.4)	0.22	0.09	0.12-0.43
D-dimer increased (>0.5 mg/L) (mg/L)	10 (28.6)	0.92	0.60	0.52-2.6
TATs normal (mg/mL)	28 (80)	2.05	0.78	1-3.5
TATs increased (>4.1 mg/mL) (mg/mL)	7 (20)	8.5	5.9	4.4-21.4
aPTT normal (s)	32 (91.4)	29.7	1.9	26.3-33.6
aPTT shortened (<26 s) (s)	3 (8.6)	24.1	0.2	23.9-24.3

Normal range for C1-INH activity, 70% to 130%. Normal range for C4, 0.20 to 0.50 g/L. Normal D-dimer, below 0.5 mg/L. Normal range for fibrinogen, 180 to 350 mg/dL. Normal range for TATs, 1 to 4.1 mg/mL. Normal range for aPTT, 26 to 36 s.

mutation p.Thr309Arg compared with the 32 patients with the mutation p.Thr309Lys.

DISCUSSION

We presented the clinical symptoms of a new and molecularly defined form of HAE. Because we observed families with male and female unaffected transmitters of HAE-FXII, it can be concluded that the mutations p.Thr309Lys and p.Thr309Arg in the factor XII gene cause the susceptibility to develop recurrent angioedema; however, angioedema will not necessarily occur in individuals with these mutations; this type of HAE has an incomplete clinical penetrance and, accordingly, it seems obvious that additional conditions are necessary to provoke the angioedema attacks in patients with HAE-FXII.

Our results reveal that the cardinal symptoms of HAE-FXII are skin swellings (mainly facial swellings) and abdominal attacks. Tongue swellings, laryngeal edemas, and swellings of the soft palate occur too, but considerably less often. Considering 1 limitation of our study, that we observed only a small number of patients with HAE-FXII, which is a rare disease, the symptomatology of HAE-FXII seems to differ from that of HAE–C1-INH, in which extremity swellings are far more frequent than facial swellings. In HAE–C1-INH, abdominal attacks are more frequent, whereas tongue swellings are only rarely observed.[18] Until now, there has been no sufficient explanation for this differing phenotypic symptom pattern. Clinical symptoms of HAE-FXII usually start in the second decade of life or later, even though they may occur earlier, as was shown in 1 patient in whom the clinical symptoms started at age 6 years. She was the only patient in whom the clinical symptoms started before menarche. In contrast, in HAE–C1-INH, about 50% of patients experience the beginning of disease within the first 10 years of life.[18,19]

A striking clinical feature of HAE-FXII is its predominance in women. It may be assumed that estrogens play an important role in the regulation of the phenotypic expression of the disease. Various strong arguments support this hypothesis:

1. Predominance of the female sex. Besides the 35 women described here, 4 women in a French family[16] and 2 women in each of 2 other French families[9,14] have been described. Only recently, an account was given of 3 men who developed swelling attacks, beginning in the sixth decade of life on average.[14]
2. Age of onset. HAE-FXII rarely occurs before puberty. Among our patients, 15 of 35 women experienced their first symptoms spontaneously—that is, without pregnancy or use of OC; in 14 of these individuals, onset took place obviously after puberty with its natural increase of estrogens.
3. Onset or worsening of clinical symptoms after intake of OC, pregnancy, or HRT—all high-estrogen states. A large percentage of women had their first clinical symptoms after the beginning of OC intake or the first pregnancy (20 of 35 patients, ie, 57.1%).
4. Limitation of the clinical symptoms to the periods of OC intake, pregnancy, or HRT in about one third of the women.
5. Positive effects of treatment with progesterone. Our results revealed that 8 women who received progesterone were symptom-free during the treatment period. Because OCs usually contain a combination of estrogen and progesterone, it seems likely that the estrogen part of the OC induced or worsened the clinical symptoms.

On the other hand, 3 points strongly argue against an exclusive role of estrogens in the occurrence of HAE-FXII symptoms: some symptoms occurred in a child before puberty, in postmenopausal women, and in a few men.[14]

Between these clear pros and cons regarding the influence of estrogens on the disease, there are also intermediate findings. In some women, the swelling attacks occurred not only during periods of high-estrogen states but also during periods in which the women were not on OCs or HRT and were not pregnant. In 3 women, all swellings occurred exclusively outside these times.

In sum, the influence of exogenous estrogens (eg, through the intake of estrogen-containing OCs or HRT) or of endogenously increased estrogen levels (eg, in pregnancy) may be strong but is variable between and within patients. Therefore, we avoid the terms “estrogen-dependent” and “estrogen-associated,” which have been created to characterize HAE with normal C1-INH.[20] In addition, a predominance of female sex is found also in HAE–C1-INH: women are more severely affected than men, on average.[18]

In the pathophysiology of angioedema attacks of HAE–C1-INH, activation of the kallikrein-kinin system (or contact system), with an increased formation of bradykinin at the end of the cascade, seems to play the most important role.[21-23] Although in HAE–C1-INH the majority of angioedema attacks occur spontaneously—that is, without a recognizable trigger factor, certain factors are likely to trigger single attacks. For example, skin swellings may follow local trauma or physical pressure, and both skin swellings and abdominal attacks may follow psychological stress or infections. Because the trigger factors are largely the same as those in HAE–C1-INH, activation of the kallikrein-kinin system and the overproduction of bradykinin also seem to be involved in the pathophysiology of angioedema attacks of HAE-FXII. Recently, we investigated FXII function, high-molecular-weight kininogen, and kallikrein-like activity in the interval between 2 attacks in patients with HAE-FXII and found them to

be not different from healthy persons.[24] Previously, an increased factor XII activity in patients with HAE-FXII was reported.[16] In the future, treatment with kallikrein inhibitors or bradykinin antagonists could help elucidate the possibility that HAE-FXII attacks are mediated by bradykinin.

A lowered function of C1-INH was reported in other patients with HAE-FXII.[9,14] Among our patients, a lower function was seen in only a minority of women. In these cases, C1-INH activity was not below 50%, as is seen in HAE–C1-INH or acquired angioedema caused by C1-INH deficiency. Low C4 concentration, increased fibrinogen, fibrin degradation products (D-dimer), TATs, and shortened aPTT have been observed also in other types of angioedema[25,26] and do not seem to be specific signs of HAE-FXII. Low C4 may be a sign of C1 esterase formation, and a shortened aPTT a sign of activation of the kallikrein-kinin system and/or lowered C1-INH activity. Elevated acute-phase protein fibrinogen may be a consequence of a stress situation, increased TATs a sign of increased thrombin formation, and increased D-dimers a sign of increased fibrinolytic activity.

Concerning treatment, corticosteroids and antihistamines turned out to be ineffective in HAE-FXII. This result is a strong indication that mast cell degranulation with histamine release is not responsible for the attacks in HAE-FXII. The number of patients treated with other drugs is still very low. It can be stated that C1-INH concentrate was effective for acute attacks, at least in most patients. Long-term prophylactic treatment with progesterone was effective in all 8 patients who received this kind of treatment. Its efficacy has also been described for HAE–C1-INH.[27] Danazol has been proven very effective in 2 of our patients; its beneficial effects in HAE–C1-INH are well known.[28] However, the mode of action of danazol in HAE–C1-INH is not clear. Recently, it has been shown that danazol plays a role in the degradation of bradykinin.[29] Long-term prophylactic treatment with tranexamic acid, an antifibrinolytic agent, has proved to be effective in 1 of our patients and in 1 patient mentioned by Bouillet et al[9] but ineffective in another patient.[14] The partial efficacy of tranexamic acid in patients with HAE-FXII indicates that an activation of the fibrinolytic system may play a role in this condition. In summary, it seems that in HAE-FXII the same drugs are effective or partially effective as those in HAE–C1-INH.

We did not find major differences concerning clinical symptoms, trigger factors, or treatments in the 3 patients with the mutation p.Thr309Arg compared with the 32 patients with the mutation p.Thr309Lys; however, the former sample is very small. For clinical practice, we recommend the performance of an analysis for the mutations in the FXII gene in patients with HAE type III—that is, patients with recurrent angioedema and normal C1-INH activity in plasma and additional family members with recurrent angioedema. If 1 of the mutations is found, examination of first-degree relatives should follow.

Clinical implications: The current description of clinical symptoms, factors that enhance edema formation, and treatment methods fosters improved diagnosis, treatment, and understanding of HAE caused by mutations in the factor XII gene.

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